

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|---|---|
| Date of mailing (day/month/year) 14 December 1999 (14.12.99) | Applicant's or agent's file reference 2025015427WO |
| International application No. PCT/US99/05131 | Priority date (day/month/year) 10 March 1998 (10.03.98) |
| International filing date (day/month/year) 09 March 1999 (09.03.99) | |
| Applicant CARROLL, Frank, Ivy | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

08 October 1999 (08.10.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|--|--|
| <p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p> | <p>Authorized officer Jean-Marie McAdams</p> <p>Telephone No.: (41-22) 338.83.38</p> |
|--|--|

PATENT COOPERATION TREATY

2025-0154-27WO

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BEAUMONT, William, E.
Oblon, Spivak, McClelland, Maier &
Neustadt, P.C.
Crystal Square Five - 4th floor
1755 Jefferson Davis Highway
Arlington, VA 22202
ÉTATS-UNIS D'AMÉRIQUE

| | |
|--|--|
| Date of mailing (day/month/year) 04 May 1999 (04.05.99) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference 2025015427WO | |
| International application No. PCT/US99/05131 | International filing date (day/month/year) 09 March 1999 (09.03.99) |
| International publication date (day/month/year) Not yet published | Priority date (day/month/year) 10 March 1998 (10.03.98) |
| Applicant CARROLL, Frank, Ivy | |

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| <u>Priority date</u> | <u>Priority application No.</u> | <u>Country or regional Office or PCT receiving Office</u> | <u>Date of receipt of priority document</u> |
|-------------------------|---------------------------------|---|---|
| 10 Marc 1998 (10.03.98) | 60/077,402 | US | 21 Apri 1999 (21.04.99) |
| 10 Nove 1998 (10.11.98) | 60/107,902 | US | 21 Apri 1999 (21.04.99) |

RECEIVED
MAY 14 1999

OBLOM, SPIVAK, McCLELLAND
MAIER & NEUSTADT, P.C.

RECEIVED IN FOREIGN FILING
DATE: 5-24-99
TIME: 10:16 A.M. PM

| | |
|---|---|
| <p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p> | <p>Authorized officer Carlos Naranjo</p> <p>Telephone No. (41-22) 338.83.38</p> |
|---|---|

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BEAUMONT, William, E.
Oblon, Spivak, McClelland, Maier &
Neustadt, P.C.
Crystal Square Five, 4th floor
1755 Jefferson Davis Highway
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

| | |
|---|--|
| Date of mailing (day/month/year) 27 June 2000 (27.06.00) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference 2025015427WO | |
| International application No. PCT/US99/05131 | International filing date (day/month/year) 09 March 1999 (09.03.99) |

| | |
|--|--|
| 1. The following indications appeared on record concerning: | |
| <input checked="" type="checkbox"/> the applicant | <input checked="" type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative |
| Name and Address | State of Nationality |
| | State of Residence |
| | Telephone No. |
| | Facsimile No. |
| 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: | |
| <input type="checkbox"/> the person <input type="checkbox"/> the name <input type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence | |
| Name and Address MASCARELLA, S., Wayne Research Triangle Institute 3040 Cornwallis Road Research Triangle Park, NC 27709- 2194 United States of America | State of Nationality US |
| | State of Residence US |
| | Telephone No. |
| | Facsimile No. |
| 3. Further observations, if necessary: Additional applicant/inventor for all designated States. A Power of Attorney signed by MASCARELLA, S., Wayne is requested. | |
| 4. A copy of this notification has been sent to: | |
| <input checked="" type="checkbox"/> the receiving Office | <input type="checkbox"/> the designated Offices concerned |
| <input type="checkbox"/> the International Searching Authority | <input checked="" type="checkbox"/> the elected Offices concerned |
| <input checked="" type="checkbox"/> the International Preliminary Examining Authority | <input type="checkbox"/> other: |

| | |
|---|----------------------------------|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Authorized officer J. Leitao |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

PATENT COOPERATION TREATY

PCT/US99/05131

Beate *Fule*

JUL 1 11 2000

OBLOM, SPIVAK, McCLELLAND
MAIER & NEUSTADT, P.C. **PCT**

From the INTERNATIONAL BUREAU

**NOTIFICATION OF THE RECORDING
OF A CHANGE**

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

2025-0154-27 WO

| | |
|--|---|
| Date of mailing (day/month/year) 27 June 2000 (27.06.00) | To: BEAUMONT, William, E. Oblon, Spivak, McClelland, Maier & Neustadt, P.C. Crystal Square Five, 4th floor 1755 Jefferson Davis Highway Arlington, VA 22202 ETATS-UNIS D'AMERIQUE |
| Applicant's or agent's file reference 2025015427WO | IMPORTANT NOTIFICATION |
| International application No. PCT/US99/05131 | International filing date (day/month/year) 09 March 1999 (09.03.99) |

| | | |
|---|---|---|
| 1. The following indications appeared on record concerning: <input checked="" type="checkbox"/> the applicant <input checked="" type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative | | |
| Name and Address <div style="border: 1px solid black; height: 100px; width: 100%;"></div> | State of Nationality <div style="border: 1px solid black; height: 100px; width: 100%;"></div> | State of Residence <div style="border: 1px solid black; height: 100px; width: 100%;"></div> |
| 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input type="checkbox"/> the person <input type="checkbox"/> the name <input type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence | | |
| Name and Address THOMAS, James, B. 1501-33 Ford Road Chapel Hill, NC 27516 United States of America | State of Nationality US | State of Residence US |
| 3. Further observations, if necessary: Additional applicant/inventor for all designated States. A Power of Attorney signed by THOMAS, James, B. is requested. | | |
| 4. A copy of this notification has been sent to: <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority </div> <div style="width: 45%;"> <input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other: </div> </div> | | |

| | |
|---|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer <div style="text-align: center;">J. Leitao</div> Telephone No.: (41-22) 338.83.38 |
|---|---|



EP B.5818 - Patentlaan 2
2280 HV Rijswijk (ZH)
+31 70 340 2040
TX 31651 epo nl
FAX +31 70 340 3016

Europäisches
Patentamt

Zweigstelle
in Den Haag
Recherchen-
abteilung

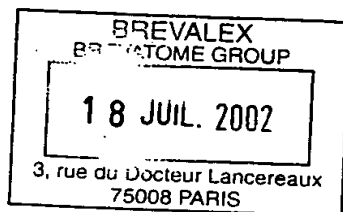
European
Patent Office

Branch at
The Hague
Search
division

Office européen
des brevets

Département à
La Haye
Division de la
recherche

Audier, Philippe André
c/o Société de Protection des Inventions,
3, rue du Docteur Lancereaux
75008 Paris
FRANCE



U.S. COPY
DOCKET NO. 220920USODiv

Datum/Date

18. 07. 2002

Zeichen/Ref./Réf.

SR 18743 US/PA

Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°.

99912345.8

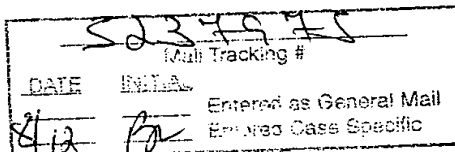
Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire

RESEARCH TRIANGLE INSTITUTE

COMMUNICATION

The European Patent Office herewith transmits

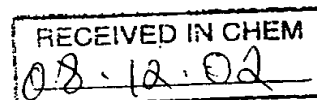
- ☐ the European search report
- ☐ the declaration under Rule 45 EPC
- ☐ the partial European search report under Rule 45 EPC
- ☒ the supplementary European search report concerning the international application under Article 157(2) EPC relating to the above-mentioned European patent application. Copies of the documents cited in the search report are enclosed.



SK
SLF01
8/9

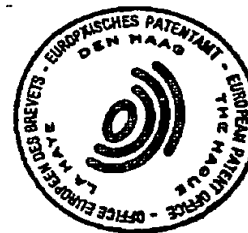
The following specifications given by the applicant have been approved by the Search Division :

- ☐ Abstract ☐ Title ☐ Figure
 - ☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.
 - ☐ The following figure will be published with the abstract, since the Search Division considers that it better characterises the invention than the one indicated by the applicant.
- Figure:
- ☒ Additional copy(copies) of the documents cited in the European search report.



REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.





European Patent
Office

**SUPPLEMENTARY
PARTIAL EUROPEAN SEARCH REPORT**

Application Number

which under Rule 45 of the European Patent Convention EP 99 91 2345
shall be considered, for the purposes of subsequent
proceedings, as the European search report

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|---|---|---|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
| A | US 5 270 328 A (CANTRELL BUDDY E ET AL) 14 December 1993 (1993-12-14) * column 2 * * claim 10 * --- | 1-5,23 | C07D211/22 A61K31/435 C07D221/22 C07D211/58 A61K31/445 C07D221/08 |
| A | US 5 319 087 A (ZIMMERMAN DENNIS M ET AL) 7 June 1994 (1994-06-07) * claim 1 * --- | 1-5,23 | |
| A | FROIMOWITZ M. ET AL.: "Phenylmorphans and Analogues: Opioid Receptor Subtype Selectivity and Effect of Conformation on Activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 9, 1992, pages 1521-1525, XP002203667 * the whole document * * page 1522; example 2D * --- | 6-10,24 11-16,25 | |
| X | | 11-16,25 | |
| Y | EP 0 018 077 A (LILLY CO ELI) 29 October 1980 (1980-10-29) * claim 1 * --- | 11-16,25 | |
| | | -/-- | |
| The supplementary search report has been based on the last set of claims valid and available at the start of the search. | | | |
| INCOMPLETE SEARCH | | | |
| The Search Division considers that the present application, or some or all of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for the following claims: Claims searched completely : Claims searched incompletely : Claims not searched : Reason for the limitation of the search: Although claims 23-26 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compounds. | | | |
| Place of search MUNICH | | Date of completion of the search 27 June 2002 | Examiner Kollmannsberger, M |
| CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document | | T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document | |

6

EPO FORM 1503 03.82 (P04C20)



| DOCUMENTS CONSIDERED TO BE RELEVANT | | | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
|-------------------------------------|---|-------------------|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | |
| Y | BERTHA, C. M. ET AL.: "Probes for arcotic Receptor-Mediated Phenomena. 20. Alteration of Opioid Receptor Subtype Selectivity of the 5-(3-Hydroxyphenyl)morphans by Application of the Message-Address Concept: Preparation of .delta.-Opioid Receptor Ligands" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 9, 1995, pages 1523-1537, XP002203668 * page 1524; examples 7,8 * | 11-16,25 | |
| Y | BERTHA, C. M. ET AL.: "A Marked Change of Receptor Affinity of the 2-Methyl-5-(3-hydroxyphenyl)morphans upon Attachment of an (E)-8-Benzylidene Moiety: Synthesis and Evaluation of a New Class of .sigma. Receptor Ligands" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 19, 1994, pages 3163-3170, XP002203669 * page 3164 - page 3165; example 4; tables 1,2 * | 11-16,25 | TECHNICAL FIELDS SEARCHED (Int.Cl.6) |
| Y | ONG, H. H. ET AL.: "Phenylmorphans Agonists-Antagonists" JOURNAL OF MEDICINAL CHEMISTRY, vol. 17, no. 1, 1974, pages 133-134, XP002203670 * examples 1-14 * | 11-16,25 | |
| | --- -/-- | | |



| DOCUMENTS CONSIDERED TO BE RELEVANT | | | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
|-------------------------------------|--|-------------------|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | |
| P,X | THOMAS J B ET AL: "A Stereoselective Synthetic Approach to N-Alkyl-4beta-methyl-5-phenyl morphans" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 40, no. 3, 15 January 1999 (1999-01-15), pages 403-406, XP004151342 ISSN: 0040-4039 * examples 1,3 * | 11-16,25 | |
| P,X | THOMAS, J. B. ET AL.: "N-substituted 9.beta.-Methyl-5-(3-hydroxyphenyl)morphans Are Opioid Receptor Pure Antagonists" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 21, 1998, pages 4143-4149, XP002203671 * page 4144; examples 5A-C * | 11-16,25 | TECHNICAL FIELDS SEARCHED (Int.Cl.6) |
| E | WO 99 33806 A (FITZPATRICK LOUIS J ;CARSON JOHN R (US); REITZ ALLEN B (US); CARMO) 8 July 1999 (1999-07-08) * claims 1,8 * * page 15 - page 20; examples * | 17-22,26 | |
| A | US 5 214 148 A (FELDMAN PAUL L ET AL) 25 May 1993 (1993-05-25) * claims * | 17-22,26 | |
| | --- -/-- | | |



Application Number
EP 99 91 2345

page 4 of 4



CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-5, 23

Compounds of structure (I) and their use in a method of binding opioid receptors

2. Claims: 6-10, 24

Compounds of structure (II) and their use in a method of binding opioid receptors

3. Claims: 11-16, 25

Compounds of structure (III) and their use in a method of binding opioid receptors

4. Claims: 17-22, 26

Compounds of structure (IV) and their use in a method of binding opioid receptors

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 99 91 2345

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| US 5270328 | A | 14-12-1993 | US 5159081 A | 27-10-1992 |
| | | | CA 2064382 A1 | 30-09-1992 |
| | | | DE 69202186 D1 | 01-06-1995 |
| | | | DE 69202186 T2 | 05-10-1995 |
| | | | EP 0506468 A1 | 30-09-1992 |
| | | | ES 2072096 T3 | 01-07-1995 |
| | | | JP 3059292 B2 | 04-07-2000 |
| | | | JP 5097807 A | 20-04-1993 |
| ----- | | | | |
| US 5319087 | A | 07-06-1994 | US 4891379 A | 02-01-1990 |
| | | | US 4992450 A | 12-02-1991 |
| | | | US 5064834 A | 12-11-1991 |
| | | | US 5422356 A | 06-06-1995 |
| | | | AT 110057 T | 15-09-1994 |
| | | | AU 596290 B2 | 26-04-1990 |
| | | | AU 1462488 A | 20-10-1988 |
| | | | CA 1321792 A1 | 31-08-1993 |
| | | | CN 88102191 A ,B | 02-11-1988 |
| | | | DE 3851081 D1 | 22-09-1994 |
| | | | DE 3851081 T2 | 16-02-1995 |
| | | | DK 204388 A | 05-01-1989 |
| | | | EG 18864 A | 29-06-1995 |
| | | | EP 0287339 A2 | 19-10-1988 |
| | | | ES 2058265 T3 | 01-11-1994 |
| | | | HU 46892 A2 | 28-12-1988 |
| | | | IE 64508 B1 | 09-08-1995 |
| | | | IL 86061 A | 15-07-1992 |
| | | | JP 2661699 B2 | 08-10-1997 |
| | | | JP 63277661 A | 15-11-1988 |
| | | | KR 9615087 B1 | 24-10-1996 |
| | | | MX 11117 A | 01-11-1993 |
| | | | NZ 224236 A | 28-08-1990 |
| | | | PH 24752 A | 01-10-1990 |
| | | | PT 87233 A ,B | 01-05-1988 |
| | | | SU 1598869 A3 | 07-10-1990 |
| | | | ZA 8802640 A | 27-12-1989 |
| ----- | | | | |
| EP 0018077 | A | 29-10-1980 | BE 882152 A1 | 10-09-1980 |
| | | | CA 1148150 A1 | 14-06-1983 |
| | | | EP 0018077 A2 | 29-10-1980 |
| | | | EP 0059989 A1 | 15-09-1982 |
| | | | FR 2451368 A1 | 10-10-1980 |
| | | | GB 2045248 A ,B | 29-10-1980 |
| | | | GB 2111976 A ,B | 13-07-1983 |
| | | | HU 179836 B | 28-12-1982 |
| | | | IT 1129740 B | 11-06-1986 |

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 99 91 2345

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2002

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| EP 0018077 | A | | JP 55124768 A | 26-09-1980 |
| | | | LU 82235 A1 | 06-06-1980 |
| | | | US 4278797 A | 14-07-1981 |
| ----- | | | | |
| WO 9933806 | A | 08-07-1999 | AU 2009799 A | 19-07-1999 |
| | | | CA 2316341 A1 | 08-07-1999 |
| | | | EP 1049676 A1 | 08-11-2000 |
| | | | JP 2001527068 T | 25-12-2001 |
| | | | WO 9933806 A1 | 08-07-1999 |
| | | | ZA 9811842 A | 23-06-2000 |
| ----- | | | | |
| US 5214148 | A | 25-05-1993 | US 5130321 A | 14-07-1992 |
| | | | US 5387688 A | 07-02-1995 |
| ----- | | | | |

PATENT COOPERATION TREATY


PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|--|--|---|
| Applicant's or agent's file reference 2025015427WO | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US99/05131 | International filing date (day/month/year) 09 MARCH 1999 | Priority date (day/month/year) 10 MARCH 1998 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant CARROLL, FRANK, IVY | | |

| |
|---|
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>6</u> sheets.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p> |
| <p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step or industrial applicability</p> <p>IV <input checked="" type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input checked="" type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p> |

| | |
|--|--|
| Date of submission of the demand 08 OCTOBER 1999 | Date of completion of this report 10 JULY 2000 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer  CHANA AULAKH |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-1235 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/05131

I. Basis of the report**1. With regard to the elements of the international application:***☒ the international application as originally filed☒ the description:

pages 1-137, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the claims:

pages 138-146, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the drawings:

pages 1-19, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig NONE

5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/05131

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. ..

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/05131

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

| | | |
|-------------------------------|------------------------------|-----|
| Novelty (N) | Claims <u>1-10 AND 16-26</u> | YES |
| | Claims <u>11-15</u> | NO |
| Inventive Step (IS) | Claims <u>1-10 AND 16-26</u> | YES |
| | Claims <u>11-15</u> | NO |
| Industrial Applicability (IA) | Claims <u>1-26</u> | YES |
| | Claims <u>NONE</u> | NO |

2. citations and explanations (Rule 70.7)

Claims 11-15 lack novelty under PCT Article 33(2) as being anticipated by Awaya et al.

Awaya discloses morphan derivatives. The compounds no. 1, 3a and 3b on page 536 of Awaya anticipate the instant claims and therefore, are detrimental to the novelty of the instant claims.

Claims 11-15 lack an inventive step under PCT Article 33(3) as being obvious over Awaya et al.

Awaya discloses morphan derivatives. The compounds 1, 3a and 3b of Awaya anticipate the instant claims and therefore, are detrimental to the inventive step of the instant claims.

Claims 1-26 meet the criteria set out in PCT Article 33(4) for industrial applicability.

_____ **NEW CITATIONS** _____

AWAYA, H. et al. Racemic and optically active 2,9-dimethyl-5-(m-hydroxyphenyl) morphans and pharmacological comparison with the 9-demethyl homologues. J. Med. Chem. 1984, Vol. 27, pages 536-539, see compounds 1, 3a, 3b on page 536.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/05131

VI. Certain documents cited**1. Certain published documents (Rule 70.10)**

| <u>Application No. Patent No.</u> | <u>Publication Date (day/month/year)</u> | <u>Filing Date (day/month/year)</u> | <u>Priority date (valid claim) (day/month/year)</u> |
|---------------------------------------|--|---|---|
| WO 98/28270 A1 | 02 JULY 1998 | 09 DECEMBER 1997 | 20 DECEMBER 1996 |

2. Non-written disclosures (Rule 70.9)

| <u>Kind of non-written disclosure</u> | <u>Date of non-written disclosure (day/month/year)</u> | <u>Date of written disclosure referring to non-written disclosure (day/month/year)</u> |
|---------------------------------------|--|--|
|---------------------------------------|--|--|

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/05131

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A61K 31/435 ; C07D 211/14, 211/56, 22/02, 221/06 and US Cl.: 514/290, 299, 329, 331; 546/101, 112, 222, 224, 234

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05131

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/435; C07D 211/14, 211/56, 221/02, 221/06
US CL :514/290, 299, 329, 331 ; 546/101, 112, 223, 224, 234

According to International Patent Classification (IPC) or to both national classification and IPC...

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/290, 299, 329, 331 ; 546/101, 112, 223, 224, 234

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X,P | THOMAS, J.B. et al. Identification of an opioid k receptor subtype-selective N-substituent for (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl) piperidine. J.Med. Chem. December 1998, Volume 41, Number 26, pages 5188-5197, especially compounds in scheme 1 on page 5189. | 1-5, 23 |
| X,P | THOMAS, J.B. et al. N-substituted octahydro-4a-(3-hydroxyphenyl)-10a-methyl-benzo[glisoquinilines are opioid receptor pure antagonists. Bioorg. & Med. Chem. Lett. December 1998, Volume 8, pages 3149-3152, especially compound 4 on pages 3149 and 3150. | 6-8, 10, 24 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *E* earlier document published on or after the international filing date | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *A* document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

| | |
|---|---|
| Date of the actual completion of the international search 16 JUNE 1999 | Date of mailing of the international search report 09 JUL 1999 |
|---|---|

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230Authorized officer
CHANA AULAKH
Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05131

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | AWAYA, H. et al. Racemic and optically active 2,9-dimethyl-5-(m-hydroxyphenyl)morphans and pharmacological comparison with the 9-demethyl homologues. J.Med. Chem. 1984, Volume 27, Number 4, pages 536-539, especially compound 3 on page 536. | 11-15, 25 |
| X,P | WO 98/28270 A1 (ASTRA PHARMA INC.) 02 July 1998, examples 2, 5, 9 and 10. | 17-22, 26 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05131

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

I. Claims 1-5 and 23, directed to compounds of formula (I) and a method of using them, classified in class 546, subclass 229+.

II. Claims 6-10 and 24, directed to compounds of formula (II) and a method of using them, classified in class 546, subclass 79+.

III. Claims 11-16 and 25, directed to compounds of formula (III) and a method of using them, classified in class 546, subclass 112+.

IV. Claims 17-22 and 26, directed to compounds of formula (IV) and a method of using them, classified in class 546, subclass 192+.

The inventions listed as Groups I, II, III and IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

There is no common core which in the Markush Practice, is a significant structural element shared by all of the alternatives ; see PCT Administrative Instructions Annex B Part I (f) (i) (B) (1).